metes and bounds of the claims are clear. A claim term is not indefinite merely because it is broad, but only if it is confusing. *See* MPEP §2173.04 (July 1998). Applicant submits that the recitation of "optional" language would not confuse the skilled artisan and, therefore, respectfully requests that the Examiner withdraw the rejection.

The Examiner has rejected claim 2 as indefinite because of the phrase "antibody subfragment." In the rejection, the Examiner questions how an antibody subfragment differs from an antibody fragment. In response to the rejection, applicant respectfully directs the Examiner to page 13, line line 29 through page 14, line 7. The specification provides, for example, that a subfragment can be a portion of an antibody fragment that retains the hypervariable, antigen-binding region of an immunoglobulin and having a size similar to or smaller than a Fab' fragment, *e.g.*, a single-chain fragment. Accordingly, the specification adequately differentiates between antibody fragments and subfragments. A withdrawal of the rejection is accordingly is solicited.

35 U.S.C. § 112, first paragraph:

The Examiner has rejected claims 1-54 on enablement grounds, asserting that "the specification does not reasonably provide enablement commensurate with the scope of the claimed invention. The Examiner argues that the claims over-broadly "read on methods of *in vivo* therapy using immunotoxins for any type of disease" (Office Action, p. 4, lines 12-13). The Examiner's basis for the rejection is that "[t]he specification... does not show data that use of the targeting constructs result in a therapeutic effect" (Office Action, p. 4, lines 16-18), and "because of the lack of working examples demonstrating the efficacy of the claimed methods, kits and preparations, it is not clear that, *in vivo*, that the localization to a target site of any of the contemplated cytotoxic agenst would result in a therapeutic effect." (emphasis added).

Even where applicant has provided actual data, the examiner appears to discredit their value. For example, the Examiner notes that, even though the specification does provide data covering the formation of targeting constructs according to the invention, there is no evidence "that targeting of a cytotoxic agent would result in a decrease in tumor mass" (Office Action, p. 5 lines 7-9). It is respectfully submitted that the Examiner's rejection is unsupported and unsustainable because applicant does not have the burden to present data to support enablement.

Applicant's specification is presumed enabling, absent objective evidence to the contrary. Furthermore, the PTO bears the initial burden of setting forth a reasonable

explanation as to why it believes that the scope of protection provided by [the] claim is not adequately enabled by the description of the invention provided in the specification. *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); *In re Marzocchi*, 439 F.2d 220, 223, 169 USPQ 367, 369 (CCPA 1971); MPEP § 706.03. The PTO must provide evidence or technical reasoning substantiating doubts regarding the enabling quality of the specification. *Id.*; MPEP § 2164.04.

Here, the Examiner cites U.S. Pat. No. 6,036,955 to Thorpe *et al.* for the proposition that "success in treating one type of disease is not necessarily predictive of success for a second type of disease." (Office Action, p. 4, lines 13-14). However, this portion of Thorpe *et al.* only relates to the alleged limitation of using immunotoxins (i.e. a tumor-direct antibody conjugated to a cytoxic agent) for treating *solid* tumors. Although applicant, at this time, does not opine on the application of the present invention to all types of "solid tumors," applicant submits that it is "not a function of the claims to specifically exclude *possible* inoperative substances." *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569 (Fed. Cir. 1984). The question is not whether all embodiments are operative; rather, the question is whether one of skill in the art could determine which ones are operative. Applicant respectfully submits that a skilled artisan would be able to discern whether the claimed methodology was effective against a target site, for example, a malignant tumor. Accordingly, Thorpe *et al.* cannot be read as supporting the Examiner's blanket enablement rejection. Accordingly, a withdrawal of the rejection is respectfully solicited.

35 U.S.C. § 102(b)

The Examiner has rejected Claim 54 under 35 U.S.C. § 102(b) as anticipated by Bosslet *et al.* Applicant submits, however, that Bosslet *et al.* is not prior art against claim 54. Although the Examiner has not accorded claim 54 an effective filing date of April 18, 1988, applicant submits that this claim is adequately supported by the disclosure as originally filed. Claim 54 recites that the targeting protein-enzyme conjugate comprises a fusion protein of the targeting protein and the enzyme." The specification of the parent application discloses at, *e.g.*, page 8, line 21 through page 9, line 14 methods to covalently link an antibody to an enzyme, which shows that the application filed April 18, 1988, discloses fusion proteins comprising a targeting protein and an enzyme. A withdrawal of the rejection is respectfully solicited.

35 U.S.C. § 103

The Examiner rejects claims 12, 14, and 15 under 35 U.S.C. § 103(a) as obvious over Sharma *et al.* or Blakey *et al.* in view of Martinis *et al.* Applicant traverses the rejection on the merits, for the reasons that follow.

To establish a *prima facie* case of obviousness, the Examiner must show not only that the art evidences a motivation to have combined the references, as posited, but also that the combination suggests all recited elements. *See* MPEP § 2142. Here, the Examiner has not made a showing that the prior art teaches or suggests all of the claimed elements. In particular, the Examiner has not shown that the prior art teaches

> "at least one multispecific targeting protein comprising at least one first binding site which specifically binds to a substance produced by or associated with the target site and present at the target site and at least one second binding site which specifically binds to an epitope on an enzyme, wherein binding between the targeting protein and the enzyme does not interfere with enzyme activity... [and wherein] the targeting protein binds the enzyme to form a targeting protein-enzyme conjugate *in situ*."

The Examiner already has stated that neither "Sharma *et al.*." nor "Blakey *et al.* ... teach methods employing targeting of enzyme to a target site using multispecific antibodies" (Office Action at p. 9, lines 3-4; p. 10, lines 5-7). The Examiner then cites Martinis *et al.* as teaching these "bispecific antibodies" (Office Action at p. 9, lines 5-6; p. 10, lines 7-9).

It is true that Martinis *et al.* teaches (1) obtaining "hybrid [bispecific] monoclonal antibodies reliably and in good yield that have not been denatured in the process of their preparation and also (2) providing "immunodiagnostic and immunotherapeutic processes which employ antibodies having a dual specificity" (page 7, lines 9-11; 14-16). However, Martinis *et al.* do not teach or suggest using a proagent-activating enzyme in this context and is silent as to the potential for using bispecific antibodies in immunoconjugates of the type described by Sharma *et al.* and Blakey *et al.* The combination of Sharma *et al.* or Blakey *et al.* with Martinis *et al.*, therefore, would not have suggested the formation of an antibody-enzyme conjugate *in situ*.

One might say that Martinis *et al.* disclose polydomas (bispecific antibodies), hybrid monoclonal antibodies that have dual specificity for two different antigenic determinants, and certain immunodiagnostic and immunotherapeutic applications. The Examiner has cited page 6, lines 18-28 as the basis for Martinis *et al.'s* alleged teaching the bispecific antibodies of the present invention. However, Martinis *et al.* do not teach or suggest the bispecific antibodies of the invention, *e.g.*, those that bind an enzyme and a determinant of a target. Instead, Martinis

et al. disclose only bispecific antibodies that bind to a target site and a therapeutic or diagnostic agent. At page 6, lines 18-28, Martinis *et al.* provide,

> ... according to the present invention there are provided processes for immunodiagnosis and immunotherapy employing antibodies having a dual specificity. Generally these processes employ a monoclonal antibody or polyclonal antibodies having a first specificity against a target antigen and a second specificity against a substance, for example, another antigen or hapten, which permits a diagnosis to made of the target antigen or which permits delivery of, or is itself, an agent which is lethal to the target antigen or the tissue with which it s associated. (emphasis added).

According to Martinis *et al.*., the "other" antigen or hapten in the above-quoted passage can be, itself, a therapeutic or diagnostic agent and, therefore, is not a precursor thereof. Thus, those very methods and reagents disclosed by Martinis *et al.* embody the problem overcome by the instant invention, namely, "deliver[ing] an effective amount of therapeutic agent to the target site while minimizing cytotoxicity to non-target cells and tissue" (p. 4, lines 11-14). Martinis *et al.*., on the other hand, provide circulating therapeutic or diagnostic agents in already active form, thereby subjecting patients to potential side effects as a result of non-localized agents.

Accordingly, Martinis *et al.* cannot be regarded as teaching the bispecific antibodies according to the present invention. Even in the most general terms, Martinis *et al.* do not embrace a bispecific antibody having (1) a specificity for a determinant of a target and (2) a second specificity for an enzyme to convert a proagent to an active agent at the target site. Accordingly, Martinis *et al.* do not recognize the advantages of the present invention, which provides, in part, for the use of a bifunctional antibody to convert a physiologically innocuous proagent into an active therapeutic or diagnostic agent at a target site. In fact, Martinis *et al.* actually teach away from the present invention, inasmuch as the teachings of Martinis *et al.* are directed entirely to direct administration of active agents that are localized at a site upon binding to a previously localized bispecific antibody.

The Examiner also has rejected claims 1, 2, 4, 5, 12, 14, 15, and 53 under 35 U.S.C. § 103(a) over Bagshawe *et al.* in view of Martinis *et al.* and further in view of Goldenberg. The Examiner relies on Bagshawe *et al.* as teaching a method of targeting CPG2 to a target site. The Examiner relies on Martinis *et al.* for essentially the same reasons as described above. Lastly, the Examiner cites Goldenberg as suggesting the use of a clearing agent, which is an optional step in the rejected method claims.

As a preliminary matter, applicant submits that the rejection of claims 1, 2, 5, and 53 in this regard is improper, inasmuch as Bagshawe *et al.* is not prior art against these claims. At

paragraph 2 of page 2, the Examiner lists the claims that allegedly are not supported by disclosure of the parent or grandparent (07/182,623). Claims 1, 2, 5, and 53 are not among this list of claims. Therefore, the effective filing date for these claims is the filing date of the grandparent application, April 18, 1988, which antedates the date of Bagshawe *et al.*, September 6, 1988. Accordingly, a withdrawal of the rejection is solicited.

In traversing the rejection of claims 4, 12, 14 and 15, applicant submits that the Examiner's reliance on Martinis *et al.* is improper for essentially the same reasons described above. None of the references that the Examiner relies upon teaches or suggests "at least one multispecific targeting protein comprising at least one first binding site which specifically binds to a substance produced by or associated with the target site and present at the target site and at least one second binding site which specifically binds to an epitope on an enzyme, wherein binding between the targeting protein and the enzyme does not interfere with enzyme activity... [and wherein] the targeting protein binds the enzyme to form a targeting protein-enzyme conjugate *in situ*."

Each of the rejections under 35 U.S.C. § 103 rests upon the determination that one of ordinary skill in the art, as a matter of law, would have been motivated to use the bispecific antibodies of Martinis *et al.* in an antibody-enzyme-prodrug application, such as that disclosed by Sharma *et al.* Blakey *et al.* or Bagshawe *et al.*, to arrive at the presently claimed invention. However, the prior art does not provide any suggestion to use bispecific antibodies to form antibody-enzyme conjugates effective for activating a proagent at a tumor site, as presently claimed. Applicant respectfully submits that the present invention is based on impermissible hindsight reconstruction, since the only reference that discloses the use of bispecific antibodies to specifically bind an enzyme and a target site *in situ* is the present application. Accordingly, the Examiner has not proven a *prima facie* case of obviousness for any of the claims.

Obviousness-type double patenting:

When the other outstanding issues have been resolved, applicant will analyze the claims to determine whether a terminal disclaimer will be necessary.

Conclusion

In view of the foregoing, applicant submits that all rejections and objections are overcome or are mooted and that the present claims are in condition for allowance. Should the Examiner have any questions regarding the present application or believe that further discussion

will advance prosecution, the Examiner is invited to contact the undersigned at the telephone number listed below.

Respectfully submitted,

Nov. 20, 2000
Date

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